In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 16-880V

Filed: March 25, 2021

RALPH PARMER, Petitioner, v. SECRETARY OF HEALTH AND HUMAN SERVICES, Respondent.	*	To Be Published Influenza ("Flu") Vaccine; Thrombotic Thrombocytopenia Purpura ("TTP")

Isaiah Kalinowski, Esq., Maglio Christopher and Toale, PA, Washington, D.C., for petitioner.
Christine Becer, Esq., U. S. Department of Justice, Washington, D.C., for respondent.

RULING ON ENTITLEMENT[1]

Roth, Special Master:

On July 25, 2016, Ralph Parmer ("Mr. Parmer" or "petitioner") timely filed a petition for compensation under the National Vaccine Injury Compensation Program, 42 U.S.C. § 300aa-10, et seq.[2] (the "Vaccine Act" or "Program"), alleging that the influenza ("flu") vaccination that petitioner received on October 14, 2013 caused him to develop thrombotic thrombocytopenia purpura ("TTP"). Petition ("Pet.") at ¶¶ 2, 7, 11-12.

[1] This Ruling has been designated "to be published," which means I am directing it to be posted on the Court of Federal Claim's website, in accordance with the E-Government Act of 2002, Pub. L. No. 107-347, 116 Stat. 2899, 2913 (codified as amended at 44 U.S.C. § 3501 note (2006)). **This means the Ruling will be available to anyone with access to the internet.** However, the parties may object to the Ruling's inclusion of certain kinds of confidential information. Specifically, under Vaccine Rule 18(b), each party has fourteen days within which to request redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). Otherwise, the whole Ruling will be available to the public. *Id*.

[2] National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755. Hereinafter, for ease of citation, all "§" references to the Vaccine Act will be to the pertinent subparagraph of 42 U.S.C. § 300aa (2012).

An entitlement hearing was held on May 2, 2019, in Washington, DC. For the reasons stated herein, I find that petitioner's evidence is sufficient to demonstrate that the flu vaccine he received on October 17, 2013 more likely than not triggered his development of TTP. Accordingly, I find that petitioner is entitled to compensation.

I. Issues to be Determined

The parties agree that petitioner was administered a flu vaccine on October 17, 2013; that there were no preexisting conditions or "intercurrent infectious exposures that bear upon causation" of petitioner's alleged injury; that petitioner has TTP, and that he had a relapse in 2014. Joint Submission ("Joint. Sub.") at 1-2, ECF No. 40. The parties disagree on the timing of onset of petitioner's TTP; whether the flu vaccine can cause TTP and, if it can, that it did so in this case. *Id*. at 2-3.

II. Background

A. Procedural History

The petition was filed on July 25, 2016. ECF No. 1. On July 26, 2016, petitioner filed medical records and medical literature in support of his claim. Petitioner's Exhibits ("Pet. Ex.") 1-19, ECF Nos. 3-6. This matter was assigned to me that same day. ECF No. 7.

During the initial status conference on September 1, 2016, petitioner's counsel advised that he planned to file additional and updated medical records as well as an affidavit from petitioner. Scheduling Order at 1, ECF No. 10. Petitioner was ordered to file his medical records, affidavit, and statement of completion by September 30, 2016. *Id*. Respondent was ordered to file a status report indicating his position by October 21, 2016. *Id*.

Petitioner filed additional medical records, his affidavit, and a Statement of Completion in September of 2016. *See* Pet. Ex. 20, ECF No. 11; Pet. Ex. 21-22, ECF No. 12; Statement of Completion, ECF No. 13.

Respondent filed a Rule 4(c) Report ("Resp. Rpt.") on February 6, 2017, recommending against compensation. Resp. Rpt. at 1, ECF No. 16.

On April 20, 2017, petitioner filed an expert report and CV from Dr. Philip Fireman. Pet. Ex. 23-24, ECF No. 20.

On August 22, 2017, respondent filed an expert report and CV from Dr. Lisa Baumann Kreuziger along with supporting medical literature. Resp. Ex. A-G, ECF No. 22; Resp. Ex. H-N, ECF No. 23.

On December 14, 2017, petitioner filed a supplemental affidavit regarding the onset of his symptoms. Pet. Ex. 25, ECF No. 26.

On July 10, 2018, an order was issued scheduling a two-day entitlement hearing for May 2 and 3, 2019. Pre-Hearing Order, ECF No. 32.

On March 6, 2019, petitioner filed his pre-hearing brief ("Pet. Brief"), along with several articles of medical literature. *See* Pet. Ex. 26-35, ECF No. 33; Pet. Ex. 36-45, ECF No. 34; Pet. Ex. 46, ECF No. 35; Pet. Brief, ECF No. 36. On March 28, 2019, respondent filed his responsive brief ("Resp. Brief") along with a supplemental report from Dr. Baumann and supporting medical literature. *See* Resp. Ex. O-P, ECF No. 37; Resp. Brief, ECF No. 38. Petitioner filed a reply brief ("Reply") on April 11, 2019. ECF No. 39. On April 18, 2019, petitioner filed a joint prehearing submission containing stipulated facts, facts in dispute, issues not in dispute, and issues remaining to be resolved. Joint. Sub., ECF No. 40.

An entitlement hearing was held in Washington, D.C., on May 2, 2019.

Post-hearing briefs were filed by both parties on July 31, 2019. Pet. Post-Hearing Brief, ECF No. 49; Resp. Post-Hearing Brief, ECF No. 50. Respondent filed an additional article of medical literature along with his post-hearing brief. *See* Resp. Ex. Q, ECF No. 50-1.

On September 19, 2019 and February 5, 2020, petitioner filed additional medical records. Pet. Ex. 47-48.3 and 54-56, ECF Nos. 51, 55. On March 11, 2020, the undersigned granted petitioner's motion for interim attorney's fees and costs. Decision, ECF No. 57.

This matter is now ripe for decision.

B. Medical History

1. Petitioner's Health Before Receiving the Influenza Vaccine

The parties agree petitioner's past medical history is noncontributory. *See generally* Pet. Ex. 3; Pet. Ex. 1 at 17.

Petitioner underwent a physical examination at Harmony Healthworks on February 17, 2012 for work. Pet. Ex. 1 at 12-25. He was 36 years old and deemed to be in good health and capable of being assigned to any work consistent with his skills and training. *Id*.

2. Petitioner's Health After Receiving the Influenza Vaccine

On October 17, 2013, petitioner, then 37 years old, received a flu vaccine at Harmony Healthworks clinic. Pet. Ex. 1 at 7.

On the evening of October 27, 2013, petitioner presented to the emergency room reporting dark urine, nausea, vomiting, abdominal pain, and shortness of breath. Pet. Ex.3 at 851, 858-59. He was noted to be asymptomatic prior to receiving a flu vaccine a week before with fatigue and weakness following the vaccine. *Id*. at 850, 861. Other records indicate that he reported not feeling well since receipt of the flu vaccine, *Id*. at 858, or between three and six days after vaccination, *Id*. at 376. His hemoglobin and platelets were low, which raised concern for a hematologic process

like TTP. *Id*. at 858-59. An intensive care unit ("ICU") physician was called to evaluate petitioner. *Id*. During this evaluation, petitioner declined rapidly, developed difficulty hearing and seizures. *Id*. at 857, 859. He was intubated and admitted to the ICU in the early morning hours of October 28, 2013. *Id*. at 255, 857.

Upon admission, petitioner was found to have acute renal failure, thrombocytopenia, anemia, and schistocytes,[3] all consistent with TTP. Pet. Ex. 3 at 255, 853. His serum level of ADAMTS13 activity, an indicator of TTP, was 19%, compared to a normal level of 67% or higher. *Id*. at 351. His treating physicians observed that this level was found after petitioner's first plasma exchange treatment, therefore his actual number prior to treatment was likely below 10%. *Id*. at 330. He was diagnosed with TTP and treated with plasmapheresis, rituximab,[4] and prednisone. *Id*. at 255. He also received dialysis treatments while hospitalized. *Id*. at 811-48. Petitioner was discharged on November 15, 2013 with a diagnosis of refractory TTP; he was prescribed two weeks of prednisone and instructed to continue plasmapheresis and rituximab on an outpatient basis. *Id*. at 255.

Petitioner's hospital records indicate that his treating physicians considered whether there was a connection between his TTP and flu shot. Pet. Ex. 3 at 348 (record dated Oct. 31, 2013, diagnosing TTP as possibly secondary to the flu shot and noting that a literature review revealed only two such reported cases); *id*. at 358 (record dated Oct. 29, 2013 noting the possibility of a vaccine reaction and discussing an autoimmune reaction to the vaccination). A hospital pharmacy record dated January 7, 2014 indicates that a flu vaccine is not indicated for petitioner due to "previous reaction to influenza vaccine." *Id*. at 1219.

Additionally, several of petitioner's medical records indicate he has an allergy to the flu shot. Pet. Ex. 3 at 271, 889; Pet. Ex. 5 at 6, 8; Pet. Ex. 21 at 5; Pet. Ex. 54 at 25; Pet. Ex. 55 at 2. Other records indicate that he has a history of flu shot induced TTP and cannot be given a flu shot. Pet. Ex. 3 at 921, 932, 938, 1184. An April 8, 2014 medical excuse note from Dr. Koenig states "TTP 2nd [secondary] to flu vaccine." Pet. Ex. 1 at 5.

Petitioner presented to Dr. Amy Castilano for follow-up care on November 22, 2013. Pet. Ex. 21 at 14. He was noted to have trace lower extremity peripheral edema and "TTP from flu shot 11/2013." *Id*. at 15. Dr. Castilano noted that petitioner's TTP was being managed by Dr. Koenig. *Id*. at 16.

On November 26, 2013, petitioner followed up with Dr. Joseph Koenig, an oncologist who treated his TTP. Pet. Ex. 2 at 12. Dr. Koenig noted that petitioner had presented four weeks earlier, "1 week after his flu vaccine," with TTP. *Id*. Dr. Koenig noted that petitioner was continuing with outpatient plasmapheresis, Rituxan, and steroids. *Id*. Petitioner was no longer having headaches,

[3] A schistocyte is a fragment of a red blood cell; it is commonly observed in people with hemolytic anemia. *Schistocyte*, DORLAND'S ILLUSTRATED MEDICAL DICTIONARY 1648 (33d ed. 2020) [hereinafter "DORLAND'S"]; *erythrocyte*, *id*. at 638.

[4] Rituximab is a monoclonal antibody which is used as an antineoplastic, a drug that checks the maturation and proliferation of malignant cells. *Rituximab*, DORLAND'S at 1624; *antineoplastic*, *id*. at 106.

seizures, or fevers, and his kidney function had returned to normal. *Id*. However, he continued to experience weakness and fatigue. *Id*.

In the months following petitioner's hospitalization, he followed up with Dr. Koenig on December 11 and December 24, 2013, and January 14, January 28, February 28, March 27, and April 28, 2014. Pet. Ex. 2 at 2-12. He was noted to have a history of TTP with "all 5 characters of the TTP pentad."[5] *Id*. at 6. He was hospitalized for ten days for inpatient plasmapheresis; he continued plasmapheresis after discharge with prednisone and eight doses of weekly Rituxan. *Id*. at 6-9, 12. At his March 27, 2014 visit, he was asymptomatic but his ADAMTS13 level was low at 40%. *Id*. at 3. Dr. Koenig reduced his prednisone and requested a consult with a TTP specialist. *Id*. At petitioner's April 28, 2014 appointment, he was off all therapy, back at work full time, and doing well. *Id*. at 2.

Petitioner was seen in the emergency room on January 16, 2014 with new onset of atrial fibrillation. Pet. Ex. 3 at 875, 902, 916-17. He complained of fatigue, shortness of breath, chest pain, and dyspnea that began "immediately after plasmapheresis this afternoon." *Id*. at 916. He had "similar symptoms during initial diagnosis of TTP." *Id*. He was diagnosed with atrial fibrillation, history of TTP, elevated thyroid-stimulating hormone, and indeterminate troponin. *Id*. at 917. He was treated with metoprolol[6] and fluids. *Id*. at 916. He was discharged the next day with instructions to follow up with a cardiologist. *Id*. at 875, 878.

The record contains a March 2014 VAERS records request relating to petitioner's October 2013 vaccination. Pet. Ex. 1 at 6, 8-10.

Petitioner underwent a physical examination with Dr. Kevin Forsyth at Harmony Healthworks on April 10, 2014 following treatment for "TTP which was attributed to his Flu shot." Pet. Ex. 1 at 2. Dr. Forsyth noted that petitioner was hospitalized for 19 days and received plasmapheresis while hospitalized and on an outpatient basis until two weeks earlier. *Id*. Petitioner reported feeling well. *Id*. His blood work was back to normal and he was not taking any medications. *Id*. His oncologist indicated he could return to work on April 14, 2014. *Id*. at 5. Dr. Forsyth determined that petitioner was able to return to work as a machine operator without restrictions. *Id*. at 4.

On September 17, 2014, petitioner was hospitalized for his first recurrence of TTP. Pet. Ex. 3 at 946-47. He presented to the emergency room with a two to three-day history of "fatigue, nausea, anorexia, and abdominal pain, which was similar to the symptoms that he had last year with his initial episode of TTP." *Id*. at 946. Bloodwork showed "marked thrombocytopenia with increased schistocytes consistent with recurrent TTP." *Id*. He was admitted to the ICU and started on plasmapheresis, prednisone, and Rituxan. *Id*. A left sided vascular catheter had been placed for plasmapheresis and was later converted to tunneled dialysis catheter. *Id*. at 947. He was discharged

[5] The five characters of the TTP pentad are severe thrombocytopenia, renal insufficiency, fever, seizures, and microangiopathic hemolytic anemia. *Thrombotic thrombocytopenia purpura*, DORLAND'S at 1534; *hemolytic-uremic syndrome*, *id*. at 1802.

[6] Metoprolol is a drug used for the treatment of angina pectoris (chest pain) and hypertension. *Metoprolol,* DORLAND'S at 1138; *angina pectoris*, *id*. at 82.

on September 23, 2014 in good condition, with prednisone and an order for weekly rituximab infusions. *Id*. at 946. His discharge diagnosis included recurrent TTP. *Id*.

At a follow up appointment on October 3, 2014, Dr. Castilano noted that petitioner had been recently discharged from the hospital for TTP. Pet. Ex. 21 at 11. He was still receiving plasmapheresis three times a week and rituximab once a week, as well as taking prednisone. *Id*.

Petitioner returned to Dr. Koenig on October 9, October 30, November 25, and December 9, 2014 and January 15, 2015. Pet. Ex. 54 at 8-12. Initially, petitioner received plasmapheresis treatments three times a week. *Id*. Dr. Koenig gradually reduced petitioner's plasmapheresis treatments and prednisone dosage before discontinuing these therapies on December 9, 2014 and January 15, 2015, respectively. *Id*. Petitioner gradually regained strength but still experienced some fatigue and weakness. *Id*. at 8. His platelet count had returned to normal and he showed no evidence of disease. *Id*.

At an appointment with Dr. Devicka Ojha on January 27, 2015, petitioner reported that he had completed plasmapheresis following his second round of TTP. Pet. Ex. 21 at 6. He was scheduled to return to work on February 24. *Id*.

On March 2, 2015, petitioner's wife called Dr. Koenig, reporting that he had returned to work on February 25, 2015 and experienced increased fatigue. Pet. Ex. 54 at 7. He had worked for two days before coming home early on February 27, 2015 and had not returned to work due to not feeling well. *Id*. Petitioner was seen by Dr. Koenig on March 3, 2015 for fatigue and weakness. *Id*. at 7. Dr. Koenig determined that he was not fully recovered and could not yet return to work. *Id*.

On April 16, 2015, petitioner returned to Dr. Koenig. Pet. Ex. 54 at 5. He reported that he was feeling better and gaining energy. *Id*. He hoped to return to work in May 2015. *Id*.

Petitioner was seen by his oncologist for follow up visits on June 16, September 16, and December 17, 2015. Pet. Ex. 54 at 2, 4-5, 28-30. He remained in remission, with a normal platelet count. *Id*. He was back at work full time and doing well. *Id*.

According to the medical records filed, petitioner required treatment for unrelated medical issues on March 10, 2017 and March 6, 2019. Pet. Ex. 48 at 5-8, 12.

On June 1, 2019, petitioner presented to the emergency room with new onset right-sided weakness. Pet. Ex. 48 at 55. On examination, his blood pressure was elevated. *Id*. at 59. He was noted to have "acute ischemic stroke symptoms" which required admission to the ICU for administration of TPA,[7] after which his symptoms resolved. *Id*. at 61, 63. He was diagnosed with thrombocytopenia with occasional schistocytes. *Id*. at 64, 225. During his hospitalization, his platelets were either below normal or at the bottom of the normal range, with levels ranging from 98 to 140, compared to a reference range of 140-440. *Id*. at 79, 80, 113, 116. He was discharged home on June 5, 2019 with diagnoses of "acute ischemic left [anterior cerebral artery] stroke

[7] "TPA" stands for tissue plasminogen activator, a protein that causes plasminogen in the bloodstream to convert to plasmin, an enzyme that causes blood clots to dissolve. *TPA*, DORLAND'S at 1914; *tissue plasminogen activator*, *id*. at 23; *plasmin*, *id*. at 1435.

secondary to paradoxical embolism," and thrombocytopenia. *Id*. at 63-66. He was prescribed several medications, including warfarin, and instructed to follow up with hematology/oncology for thrombocytopenia. *Id*. at 64-66.

On June 10, 2019, petitioner was seen by Dr. Joel Shackson to follow up after his recent hospitalization. Pet. Ex. 47 at 6-7. He was doing well, with no residual neurologic deficits. *Id*. at 10. Dr. Shackson ordered labs to ensure that his platelet count was stable and directed petitioner to return in six months. *Id*. at 11.

Petitioner returned to Dr. Koenig on June 27, 2019. Pet. Ex. 54 at 33. Dr. Koenig noted that, while hospitalized, petitioner's platelet count was low and his bloodwork showed abnormalities, but that he did not definitively have TTP. *Id*. Dr. Koenig noted that the stroke appeared to have been caused by a blood clot in petitioner's leg that traveled to his brain. *Id*. at 33, 37. Dr. Koenig concluded that the clot appeared to be unprovoked and thus recommended long term anticoagulation therapy. *Id*. at 37. Dr. Koenig planned to do further studies to check for evidence of TTP but considered this unlikely based on petitioner's bloodwork. *Id*.

Petitioner suffered another recurrence of TTP in January 2020. Pet. Ex. 55 at 13. He presented to the emergency room on January 3, 2020 with possible stroke symptoms and right-hand numbness that started two days earlier. *Id*. at 6, 13. Initially, there was concern for a stroke with no evidence of recurrent TTP. *Id*. at 19, 21. However, subsequent blood work showed low platelet levels and elevated LDH[8] levels, and on January 7, 2020, he was given a working diagnosis of TTP. *Id*. at 9, 13, 19, 25-26. Plasma exchange was initiated, and petitioner showed improvement after five treatments. *Id*. at 13, 26, 53. He was discharged on January 11, 2020, with ADAMTS13 results pending. *Id*. at 13, 15.

Petitioner followed up with Dr. Dasgupta, his primary care provider, on January 13, 2020. Pet. Ex. 56 at 13. He continued to improve. *Id*. at 17.

At a follow up with Dr. Koenig on January 14, 2020, Dr. Koenig noted that during petitioner's recent hospitalization, an MRI showed acute infarcts in the left side of his brain consistent with his symptoms. Pet. Ex. 54 at 39. His ADAMTS13 level was suppressed at less than 5%, which in Dr. Koenig's opinion, verified TTP as the working diagnosis. *Id*. at 39, 42, 80. Dr. Koenig repeated petitioner's requirement for long-term anticoagulation therapy. *Id*. at 39.

No further medical records have been filed at this time.

C. Affidavit and Testimony of Petitioner, Ralph Parmer

Petitioner submitted two affidavits in this matter and testified at hearing. *See* Pet. Ex. 22; Pet. Ex. 25.

[8] "LDH" stands for lactate dehydrogenase, an enzyme found in cells throughout the body; elevated LDH levels can indicate multiorgan injury, such as myocardial infarction, red blood cell diseases, and diffuse autoimmune inflammatory diseases. *See Mosby's Manual of Diagnostic and Laboratory Tests* 293-95 (Pagana eds., 6th ed. 2018) [hereinafter "*Mosby's*"].

Petitioner's first affidavit stated that he received the flu vaccination on October 14, 2013. Pet. Ex. 22 at ¶ 2. In his second affidavit, petitioner stated that he received the flu vaccination on October 17, 2013. Pet. Ex. 25 at ¶ 2. He recalled previously receiving a flu shot in 2012. Tr. 9. He also had the flu virus before, although he could not recall when. Tr. 9.

Petitioner testified that for the first couple of days after his October 17, 2013 flu vaccine, he felt fine. Tr. 23. He initially stated that his symptoms began three days after vaccination, but later testified that he began to feel fatigued a week after vaccination. Tr. 10, 24. He then clarified that he began to feel "off" three days after vaccination, but at that point did not experience severe symptoms until about a week after vaccination. Tr. 25-26, 28.

In 2013, petitioner was a machine operator at Alcoa (now known as Arconic) Tr. 7. It is a very physical and demanding job, requiring a high level of awareness. Tr. 7, 10. Petitioner testified that following his flu vaccine he was not able to perform his job at his usual performance level and felt a "noticeable drop" in his level of energy. Tr. 10; Pet. Ex. 25 at ¶ 3. He became fatigued halfway through a work task that he could normally complete in 25 minutes. Tr. 11, 24. However, he was not sick enough to require medical treatment. Tr. 11. At this point, he was not in pain but was experiencing discomfort and flu-like symptoms. Tr. 12.

It was not until a week after vaccination that he realized that his condition may not resolve on its own. Tr. 25-26. At the one-week point, petitioner developed stomach pain, lightheadedness, and dark, discolored urine. Tr. 13, 26; Pet. Ex. 25 at ¶ 4. He had to stop working to catch his breath, and his heart was racing. *Id*. He stated, "I felt like I was slowly dying." Pet. Ex. 25 at ¶ 4. He then developed severe headaches and mental confusion. *Id*. He testified that his symptoms continued to worsen until he went to the hospital. Tr. 27.

Petitioner described October 27, 2013 as the day his body began to shut down. Pet. Ex. 25 at ¶ 5. On that day, he was feeling fatigued but was well enough to watch football with his brother and friends. Tr. 13; Pet. Ex. 25 at ¶ 5. However, while sitting on the couch he experienced abdominal pain severe enough to cause him to double over. Pet. Ex. 25 at ¶ 5. His family members became concerned about him, and, after several requests, he agreed to go to the emergency room. Tr. 14.

His wife and brother drove him to the emergency room. Tr. 15. On the way to the hospital, he slipped in and out of consciousness; later, he "was informed that this was due to the fact [his] internal organs were shutting down." Pet. Ex. 25 at ¶¶ 5-6; Tr. 15. He remembered little from the emergency room, other than not being able to hear a doctor who was speaking to him. *Id*. at ¶ 6. He also recalled one of the doctors observing that his eyes were getting glossy and his lips were turning purple. Tr. 16. After that, petitioner deteriorated and was later told he had a grand mal seizure. Tr. 17. He was admitted to the ICU and regained consciousness about five days later. Tr. 17.

Petitioner stated that his doctors did not expressly say that his TTP was caused by the flu shot, but that he believed they considered it a possibility. Tr. 18. He testified that his treating physician, Dr. Koenig, advised him not to receive flu shots in the future, and he received this advice from other physicians as well. Tr. 18.

Petitioner testified that he was hospitalized for approximately three weeks, and continued plasmapheresis and Rituxan treatments on an outpatient basis after being discharged. Tr. 19. He did not return to work until April 2014. Tr. 20.

After returning to work, petitioner worked for about five months before he noticed the return of symptoms similar to those he experienced in 2013. Tr. 20; Pet. Ex. 25 at ¶ 8. He recognized that he was experiencing TTP symptoms and sought treatment earlier, resulting in a shorter hospitalization. Tr. 20. He was diagnosed with and treated for recurrent TTP. Pet. Ex. 25 at ¶ 8. At the time of the hearing, he testified that he had not experienced any additional TTP recurrences since the fall of 2014. [9] Tr. 21. However, he had missed a lot of work due to his TTP; as a result, he missed out on promotions and raises. Tr. 21.

Petitioner submitted that he "sustained an immunologic-hematologic injury (diagnosed and treated as thrombotic thrombocytopenic purpura) and its sequelae, which were actually caused by the vaccine administered, and [he] suffered the residual effects or complications of the above condition for more than six months following the administration of that vaccination." Pet. Ex. 22 at ¶ 3; Pet. Ex 25 at ¶ 7.

III. The Experts

A. Petitioner's Expert, Dr. Philip Fireman

On April 20, 2017, petitioner filed an expert report and curriculum vitae from Dr. Philip Fireman. Pet. Ex. 23-24. Dr. Fireman also testified at hearing.

Dr. Fireman earned a medical degree from the University of Chicago. Pet. Ex. 24 at 2. He completed his residency in pediatrics at the Children's Hospital of Pittsburgh, then performed two two-year fellowships in allergy and immunology at the National Institutes of Allergy, Immunology and Infectious Diseases Laboratory and Harvard University and Children's Hospital. *Id*. He is board certified in pediatrics and allergy and immunology. *Id*. at 3. He served as a professor at the University of Pittsburgh School of Medicine and as the director of the allergy and immunology division at the Children's Hospital of Pittsburgh for much of his career. *Id*. at 2. He has received numerous honors and authored over 100 publications, including articles on the immune effects of vaccines and the immune system's interaction with the flu virus. *Id*. at 4-27; Tr. 39.

Most of Dr. Fireman's clinical practice is focused on patients with allergies and respiratory issues. Tr. 36, 73. He has treated approximately five TTP patients in his career, some during his internship or residency. Tr. 74.

B. Respondent's Expert, Dr. Lisa Baumann Kreuziger

[9] Petitioner's June 2019 hospitalization for a stroke and January 2020 hospitalization for TTP recurrence occurred after the hearing.

Respondent filed an expert report from Dr. Lisa Baumann Kreuziger[10] on August 22, 2017, along with her curriculum vitae and medical literature. Resp. Ex. A-N. On March 28, 2019, Dr. Baumann filed a supplemental expert report and additional medical literature. Resp. Ex. O, P. Dr. Baumann also testified at hearing.

Dr. Baumann earned a medical degree from the University of Wisconsin-Madison and a master's degree in public health from the University of Minnesota. Resp. Ex. B at 2. She completed a residency in internal medicine at the Mayo Clinic and a three-year fellowship in hematology, oncology, and transplant medicine at the University of Minnesota. *Id*. at 2-3. She serves as the Associate Medical Director for the Blood Center of Wisconsin and is an Assistant Professor with the Medical College of Wisconsin in the Department of Hematology and Oncology and the Clinic and Translational Science Institute. *Id*. at 3. She is board certified in internal medicine, hematology, and medical oncology, and is the recipient of numerous awards. *Id*. Dr. Baumann specializes in "taking care of patients with bleeding and clotting problems and many autoimmune diseases of the blood, including TTP." Tr. 114. She sees approximately "five to ten new patients with TTP every year" and follows up with patients periodically to ensure that they do not have any relapses. Tr. 115.

IV. Overview of TTP

TTP is a life-threatening occlusive[11] disorder characterized by systemic platelet clumping, organ ischemia, profound thrombocytopenia (a low blood platelet count), and fragmentation of red blood cells. Resp. Ex. P at 2[12]. Patients with TTP also present with "neurologic abnormalities such as headache, confusion, focal deficits, seizures or coma" as well as hematuria, proteinuria, renal failure, and abdominal pain (with or without evidence of pancreatitis). Resp. Ex. L at 3-4[13]; *see also* Pet. Ex. 33 at 1[14] (Noting that TTP is "classically identified by a clinical "pentad" consisting of thrombocytopenia, microangiopathic hemolytic anemia, renal failure, fever, and fluctuating neurological signs"). "Although the onset of disease is often sudden, prodromal[15] manifestations (including fatigue, arthralgia, myalgia and abdominal or lumbar pain) that suggest a flu-like

[10] Dr. Baumann Kreuziger was referred to as "Dr. Baumann" during the hearing, so that is the name used throughout this Ruling.

[11] "Occlusive" means "pertaining to or causing occlusion." *Occlusive*, DORLAND'S at 1293. An occlusion is an obstruction. *Occlusion*, *id*. at 1292.

[12] Johanna A. Kremer Hovinga et al., *Thrombotic Thrombocytopenic Purpura*, 3 NAT. REV. DIS. PRIMERS 1-17 (2017), filed as "Resp. Ex. P."

[13] Han-Mou Tsai, *Pathophysiology of Thrombotic Thrombocytopenic Purpura*, 91 INT. J. HEMATOL. 1-19 (2010), filed as "Resp. Ex. L."

[14] Nobuharu Kosugi et al., *Influenza A Infection Triggers Thrombotic Thrombocytopenic Purpura by Producing the Anti-ADAMTS13 IgG Inhibitor*, 49 INTER. MED. 689-93 (2010), filed as "Pet. Ex. 33."

[15] "Prodromal" means "premonitory" or "precursor." A prodromal symptom is one indicating the onset of a disease. *Prodrome*, DORLAND'S at 1499.

episode are frequently reported at the time of diagnosis or during the preceding days." Resp. Ex. P at 6.

TTP occurs when a person has a severe deficiency in ADAMTS13 activity. Resp. Ex. P at 2. ADAMTS13 is an enzyme that cleaves[16] von Willebrand factor ("vWF") multimers.[17] *Id*. VWF is a protein that helps with platelet adhesion and aggregation at sites of vessel injury. Resp. Ex. L at. 4. In the absence of ADAMTS13, unusually large multimers of vWF accumulate in the blood and bind to platelets to form microthrombi,[18] or small blood clots. Resp. Ex. P at 2; Resp. Ex. G at 4[19]. These microthrombi circulate throughout the blood stream; they pick up "stray" platelets, which causes low platelet levels. Resp. Ex. P at 5. The microthrombi also destroy red blood cells, leading to hemolytic anemia, and cause blockages in circulation, leading to organ ischemia, or lack of blood flow to organs. *Id*.

There are two types of TTP. In congenital TTP ("cTTP"), the ADAMTS13 deficiency is caused by a genetic mutation. Resp. Ex. P at 3. In acquired, or immune-mediated, TTP[20], the ADAMTS13 deficiency is caused by autoantibodies that inhibit the activity of ADAMTS13. Pet. Ex. 27 at 1[21]; Resp. Ex. P at 5.

A curious phenomenon referred to as "sub-clinical TTP" has been described, wherein patients have profound ADAMTS13 deficiencies, but no clinical manifestations usually associated with TTP. Resp. Ex. L at 14. This deficiency is thought to be due to either mutations of the ADAMTS13 gene or persistent autoantibodies to ADAMTS13. *Id*. Cases of sub-clinical TTP vary in presentation and pathophysiology; some patients have an ADAMTS13 level slightly above "the threshold level of platelet aggregation," while others have "subclinical platelet aggregation which is masked by bone marrow compensation." *Id*. Some patients remain asymptomatic but develop chronic renal failure due to "repeated renal insult by subclinical microthrombi." *Id*. at 15. Occasionally, a patient with subclinical TTP "may present with acute thrombotic complications such as strokes without obvious precipitating events." *Id*. Patients with subclinical TTP "have extremely high risk of thrombotic complications" when exposed to conditions such as pregnancy,

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[16] "Cleave" means split or separate, as by cutting. *Cleaved*, DORLAND'S at 365.

[17] A multimer is a protein molecule made up of more than one polypeptide chain. *Multimer*, DORLAND'S at 1171.

[18] "Thrombi" is the plural of "thrombus," which means blood clot. *Thrombi*, DORLAND'S at 1892; *thrombus*, *id*. at 1893.

[19] Eric Mariotte et al., *Epidemiology and Pathophysiology of Adulthood-Onset Thrombotic Microangiopathy with Severe ADAMTS13 Deficiency (Thrombotic Thrombocytopenic Purpura): A Cross-Sectional Analysis of the French National Registry for Thrombotic Microangiopathy*, 3 LANCET HAEMATOL. e237-45 (2016), filed as "Resp. Ex. G."

[20] Immune-mediated TTP is typically referred to as "iTTP" in order to distinguish it from cTTP. However, as only immune-mediated TTP is at issue in this Ruling, all references to "TTP" herein refer to immune-mediated TTP.

[21] Christoph Klaus et al., *Epitope Mapping of ADAMTS13 Autoantibodies in Acquired Thrombotic Thrombocytopenic Purpura*, 103 BLOOD 4514-19 (2004), filed as "Pet. Ex. 27."

surgery, trauma, fever, or infection, and require prophylactic measures to raise the ADAMTS13 level to prevent complications. *Id*. at 14.

Acquired TTP has been described in association with other immune-mediated disorders, such as systemic lupus erythematosus, rheumatoid spondylitis, polyarteritis, and Sjogren's syndrome, all diseases involving vasculitis of the small blood vessels. Pet. Ex. 38 at 1[22]; Resp. Ex. P at 3. A French study examining patients with adult-onset TTP found that, of patients who did not have any associated clinical situation (i.e., infections, pregnancy, cancer, organ transplantation, drugs, or pre-existing autoimmune disease) approximately 91% of acquired TTP cases were autoimmune. Resp. Ex. G at 2, 8. In contrast, TTP associated with sepsis, cancer, bone marrow or organ transplantation, drugs, or HIV infection had features distinct from autoimmune disease associated TTP. *Id*. at 9. TTP has also been reported in association with bacterial, viral, mycoplasma, and fungal infections and following vaccinations. Pet. Ex. 38 at 2-3.

TTP affects adults between the third and fifth decades of life. Resp. Ex. P at 2. "[B]lack (African Americans or African Caribbeans) individuals and women are more frequently affected than non-black individuals and men . . .." *Id*. Black individuals may also be genetically predisposed to developing anti-ADAMTS13 autoantibodies. *Id*. at 3. HLA-DRB1*04, a genetic allele, is hypothesized to have a protective effect against TTP; this allele is less prevalent in black individuals, which "might contribute to their higher susceptibility to develop TTP." *Id*.

V. Causation and Analysis

A. Legal Standard Regarding Causation

The Vaccine Act provides two avenues for petitioners to receive compensation.[23] First, a petitioner may demonstrate a "Table" injury—i.e., an injury listed on the Vaccine Injury Table that occurred within the provided time period. 42 U.S.C. § 300aa-11(c)(1)(C)(i). "In such a case, causation is presumed." *Capizzano v. Sec'y of Health & Human Servs*., 440 F.3d 1317, 1320 (Fed. Cir. 2006); *see* § 13(a)(1)(B). Second, where the alleged injury is not listed on the Vaccine Injury Table, a petitioner may demonstrate an "off-Table" injury, which requires that the petitioner "prove by a preponderance of the evidence that the vaccine at issue caused the injury." *Capizzano*, 440 F.3d at 1320; *see* § 11(c)(1)(C)(ii). A petitioner need not show that the vaccination was the sole cause, or even the predominant cause, of the alleged injury; showing that the vaccination was a "substantial factor" and a "but for" cause of the injury is sufficient for recovery. *Pafford v. Sec'y of Health & Human Servs*., 451 F.3d 1352, 1355 (Fed. Cir. 2006); *Shyface v. Sec'y of Health & Human Servs*., 165 F.3d 1344, 1352 (Fed. Cir. 1999). Petitioners are not required "to eliminate alternative causes as part of establishing [their] prima facie case." *Doe v. Sec'y of Health & Human Servs*., 601 F.3d 1349, 1357-58 (Fed. Cir. 2010); *see Walther v. Sec'y of Health & Human Servs*., 485 F.3d 1146, 1152 (Fed. Cir. 2007) (holding that a "petitioner does not bear the burden of

[22] Peter B. Neame, *Immunologic and Other Factors in Thrombotic Thrombocytopenic Purpura (TTP)*, 6 SEMIN. THROMB. HEMOST. 416-29 (1980), filed as "Pet. Ex. 38."

[23] The Vaccine Act also requires petitioners to show by preponderant evidence that the "residual effects or complications" of the alleged vaccine-related injury lasted for more than six months. § 11(c)(1)(D)(i). It is undisputed that this six-month requirement is satisfied in this case.

eliminating alternative independent potential causes"). Once a petitioner has proven causation by preponderant evidence, "the burden then shifts to the respondent to show by a preponderance of the evidence that the injury is due to factors unrelated to the administration of the vaccine." *Deribeaux ex rel. Deribeaux v. Sec'y of Health & Human Servs*., 717 F.3d 1363, 1367 (Fed. Cir. 2013) (citing 42 U.S.C. § 300aa-13(a)(1)(B)).

To prove causation, petitioners must satisfy the three-pronged test established in *Althen v. Sec'y of Health & Human Servs*., 418 F.3d 1274 (Fed. Cir. 2005). *Althen* requires that petitioners show by preponderant evidence that a vaccination petitioner received caused their injury "by providing: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." *Id*. at 1278. Together, these prongs must show "that the vaccine was 'not only a but-for cause of the injury but also a substantial factor in bringing about the injury.'" *Stone v. Sec'y of Health & Human Servs*., 676 F.3d 1373, 1379 (Fed. Cir. 2012) (quoting *Shyface*, 165 F.3d at 1352-53). Causation is determined on a case-by-case basis, with "no hard and fast per se scientific or medical rules." *Knudsen v. Sec'y of Health & Human Servs*., 35 F.3d 543, 548 (Fed. Cir. 1994). Petitioners are not required to identify "specific biological mechanisms" to establish causation, nor are they required to present "epidemiologic studies, rechallenge, the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities." *Capizzano*, 440 F.3d at 1325 (quoting *Althen*, 418 F.3d at 1280). "[C]lose calls regarding causation are resolved in favor of injured claimants." *Althen*, 418 F.3d at 1280.

Each of the *Althen* prongs requires a different showing. Under the first *Althen* prong, petitioner must provide a "reputable medical theory" demonstrating that the vaccine received can cause the type of injury alleged. *Pafford*, 451 F.3d at 1355-56 (citation omitted). To satisfy this prong, petitioner's "theory of causation must be supported by a 'reputable medical or scientific explanation.'" *Andreu*, 569 F.3d at 1379 (quoting *Althen*, 418 F.3d at 1278). This theory need only be "legally probable, not medically or scientifically certain." *Id*. at 1380 (emphasis omitted) (quoting *Knudsen*, 35 F.3d at 548). Nevertheless, "petitioners [must] proffer trustworthy testimony from experts who can find support for their theories in medical literature." *La Londe v. Sec'y of Health & Human Servs.*, 746 F.3d 1334, 1341 (Fed. Cir. 2014).

The second *Althen* prong requires proof of a "logical sequence of cause and effect." *Capizzano*, 440 F.3d at 1326 (quoting *Althen*, 418 F.3d at 1278). Even if the vaccination can cause the injury, petitioner must show "that it did so in [this] particular case." *Hodges v. Sec'y of Health & Human Servs*., 9 F.3d 958, 962 n.4 (Fed. Cir. 1993) (citation omitted). "A reputable medical or scientific explanation must support this logical sequence of cause and effect," *id*. at 961 (citation omitted), and "treating physicians are likely to be in the best position to determine whether a logical sequence of cause and effect show[s] that the vaccination was the reason for the injury," *Paluck v. Sec'y of Health & Human Servs*., 786 F.3d 1373, 1385 (Fed. Cir. 2015) (quoting *Andreu*, 569 F.3d at 1375).

However, medical records and/or statements of a treating physician's view do not per se bind the special master to adopt the conclusions of such an individual, even if they must be considered and carefully evaluated. Section 12(b)(1)(providing that "[a]ny such diagnosis,

conclusion, judgment, test result, report or summary shall not be binding on the special master or court."); *Snyder v. Sec'y of Health & Human Servs*., 88 Fed. Cl. 706, 746 n.67 (2009)("there is nothing…that mandates that the testimony of a treating physician is sacrosanct—that it must be accepted in its entirety and cannot be rebutted"). As with expert testimony offered to establish a theory of causation, the opinions or diagnoses of treating physicians are only as trustworthy as the reasonableness of their suppositions or bases. The views of treating physicians should also be weighed against other, contrary evidence also present in the record – including conflicting opinions among such individuals. *Hibbard v. Sec'y of Health & Human Servs*., 100 Fed. Cl. 742, 749 (2011) (determining it is not arbitrary or capricious for a special master to weigh competing treating physicians' conclusions against each other), *aff'd*. 698 F.3d 1355 (Fed. Cir. 2012); *Caves v. Sec'y of Health & Human Servs*., 100 Fed. Cl. 119, 136 (2011), *aff'd*, 463 Fed. Appx. 932 (Fed. Cir. 2012); *Veryzer v. Sec'y of Health & Human Servs*., No. 06-522V, 2011 WL 1935813, at *17 (Fed. Cl. Spec. Mstr. Apr. 229, 2011), *mot. for review den'd*, 100 Fed. Cl. 344 (Sept. 29, 2011), *aff'd*, 475 Fed. Appx. 765 (Fed. Cir. 2012).

The third *Althen* prong requires that petitioner establish a "proximate temporal relationship" between the vaccination and the alleged injury. *Althen*, 418 F.3d at 1281. This "requires preponderant proof that the onset of symptoms occurred within a timeframe for which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." *De Bazan v. Sec'y of Health & Human Servs*., 539 F.3d 1347, 1352 (Fed. Cir. 2008). Typically, "a petitioner's failure to satisfy the proximate temporal relationship prong is due to the fact that onset was too late after the administration of a vaccine for the vaccine to be the cause." *Id*. However, "cases in which onset is too soon" also fail this prong; "in either case, the temporal relationship is not such that it is medically acceptable to conclude that the vaccination and the injury are causally linked." *Id*.; *see also Locane v. Sec'y of Health & Human Servs*., 685 F.3d 1375, 1381 (Fed. Cir. 2012) ("[If] the illness was present before the vaccine was administered, logically, the vaccine could not have caused the illness.").

B. Evaluating Expert Testimony

Establishing a sound and reliable medical theory often requires a petitioner to present expert testimony in support of his claim. *Lampe v. Sec'y of Health & Human Servs*., 219 F.3d 1357, 1361 (Fed. Cir. 2000). Vaccine Program expert testimony is usually evaluated according to the factors for analyzing scientific reliability set forth in *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 594-96 (1991).[24] *Cedillo v. Sec'y of Health & Human Servs*., 617 F.3d 1328, 1339 (Fed. Cir. 2010) (citing *Terran v. Sec'y of Health & Human Servs*., 195 F.3d. 1302, 1316 (Fed. Cir. 1999)).

The *Daubert* factors are usually employed by judges in the performance of their evidentiary gatekeeper roles to exclude evidence that is unreliable and/or could confuse the jury. In Vaccine Program cases, by contrast, these factors are used in the weighing of the reliability of scientific

[24] The *Daubert* factors for analyzing the reliability of testimony are: (1) whether a theory or technique can be (and has been) tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) whether there is a known or potential rate of error and whether there are standards for controlling the error; and (4) whether the theory or technique enjoys general acceptance within a relevant scientific community." *Terran*, 195 F.3d at 1316 n.2 (citing *Daubert*, 509 U.S. at 592-95).

evidence proffered. *Davis v. Sec'y of Health & Human Servs*., 94 Fed. Cl. 53, 66-67 (2010) ("uniquely in this Circuit, the *Daubert* factors have been employed also as an acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted"). The flexible use of the *Daubert* factors to evaluate the persuasiveness of expert testimony has routinely been upheld. *See, e.g., Snyder*, 88 Fed. Cl. at 742-45. In this case, as in numerous other Vaccine Program cases, *Daubert* has not been employed to determine what evidence should be admitted, but rather to determine whether expert testimony offered is reliable and/or persuasive.

Where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen v. Sec'y of Health & Human Servs*., 618 F.3d 1339, 1347 (Fed. Cir. 2010) (citing *Lampe*, 219 F.3d at 1362). However, nothing requires the acceptance of an expert's conclusion, "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder*, 88 Fed. Cl. at 743 (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997)); *see also Isaac v. Sec'y of Health & Human Servs*., No. 08-601V, 2012 WL 3609993, at *17 (Fed. Cl. Spec. Mstr. July 30, 2012), *mot. for review den'd*, 108 Fed. Cl. 743 (2013), *aff'd*, 540 F. App'x. 999 (Fed. Cir. 2013) (citing *Cedillo*, 617 F.3d at 1339). Weighing the relative persuasiveness of competing expert testimony, based on a particular expert's credibility, is part of the overall reliability analysis to which special masters must subject expert testimony in Vaccine Program cases. *Moberly*, 592 F.3d at 1325-26 ("[a]ssessments as to the reliability of expert testimony often turn on credibility determinations"); *see also Porter v. Sec'y of Health & Human Servs*., 663 F.3d 1242, 1250 (Fed. Cir. 2011) ("this court has unambiguously explained that special masters are expected to consider the credibility of expert witnesses in evaluating petitions for compensation under the Vaccine Act.").

C. Consideration of Medical Literature

Finally, although this decision discusses some but not all of the literature which was submitted by the parties, the undersigned reviewed and considered all of the medical records and literature submitted in this matter. *See Moriarty ex rel. Moriarty v. Sec'y of Health & Human Servs*., 844 F.3d 1322, 1328 (Fed. Cir. 2016) ("We generally presume that a special master considered the relevant record evidence even though [s]he does not explicitly reference such evidence in h[er] decision."); *Simanski v. Sec'y of Health & Human Servs*., 115 Fed. Cl. 407, 436 (2014) ("[A] Special Master is 'not required to discuss every piece of evidence or testimony in her decision.'" (citation omitted)), *aff'd*, 601 F. App'x 982 (Fed. Cir. 2015).

D. Analysis

As a preliminary matter, the experts in this case agree more than they disagree. They agree that TTP is immune mediated and that TTP has various causes, including infections. Pet. Ex. 23 at 4; Resp. Ex. A at 3-4. They agree that it is medically appropriate for TTP to occur within a week of exposure to a cause. Tr. 137, 141-42. They disagree that influenza vaccine can cause TTP and they disagree that petitioner's TTP was caused by his influenza vaccine. Joint Sub. at 3.

Application of the *Althen* prongs reveals the following: (1) petitioner has offered a persuasive medical theory; (2) the theory provided is applicable to the facts of petitioner's case;

and (3) petitioner has established a medically acceptable timeframe in which his symptoms could have begun or developed.

1. Petitioner Has Articulated a Medical Theory Causally Connecting Flu Vaccine to TTP

To satisfy *Althen* Prong I, petitioner must present a "sound and reliable medical or scientific explanation" causally connecting the vaccine to her alleged injuries. *Knudsen,* 35 F.3d at 548.

The parties agree that TTP is an autoimmune disorder that occurs as a result of the "dysregulation of the balance between ADAMTS-13 protease (an enzyme) and its natural target, von Willebrand factor (VWF), leading to unrelated clotting by the VWF into multimers, resulting thrombi which can cause organ damage, failure, and death." Joint Sub. at 2, citing Pet. Ex. 23 at 4; Resp. Ex. A at 3. The parties agree that TTP can be differentiated into congenital TTP and immune-mediated, formerly termed "idiopathic" TTP. Joint Sub. at 2. The parties further agree that "acquired TTP is the result of an auto-immune reaction against ADAMTS-13," that ITP is a different autoimmune disorder that leads to thrombocytopenia, and "that ITP is distinct from TTP in the specific pathologic mechanism of injury that results in thrombocytopenia." *Id*.

The parties disagree on whether petitioner has offered preponderant evidence that the flu vaccine is capable of triggering the immune response leading to TTP. Petitioner's theory is that the flu vaccine is capable of triggering an immune response that leads to TTP via molecular mimicry. Respondent contends that to succeed, petitioner "should have to produce some evidence that the flu vaccine can cause the production of ADAMTS13 antibodies." Resp. Post-Hearing Brief at 5. Respondent asserts that neither expert testified to any homology or similarities between the flu vaccine and ADAMTS13. *Id*. at 6. Thus, respondent argues, petitioner cannot prevail.

i. Petitioner submits that the flu vaccine could trigger immune-mediated TTP via molecular mimicry

Dr. Fireman testified that in his opinion, the flu vaccine could "play a significant causal role" in initiating or triggering immune-mediated TTP. Pet. Ex. 23 at 9; Tr. 50-51. He based this opinion on case reports and medical literature. Tr. 95-96.

Dr. Fireman explained that TTP results from an immunologic trigger that negatively affects immune tolerance of ADAMTS13, resulting in an autoimmune or cross-reactive immune response. Pet. Ex. 23 at 6-7. At hearing, Dr. Fireman agreed with a study on the pathophysiology of TTP which stated that "characteristics of the ADAMTS13 inhibitors suggest that the immune response is induced by exposure to exogeneous antigens with molecular mimicry to ADAMTS13." Tr. 47-48, quoting Resp. Ex. L at 11.

He testified that, although there are theories, it is currently unknown how antibodies to ADAMTS13 develop. Tr. 44-45; Pet. Ex. 27 at 1 ("ADAMTS13 inhibitors have not been fully characterized at the molecular level"), *id*. at 4 ("[T]he epitope specificity of such antibodies [to ADAMTS13] has not been analyzed in detail"). Dr. Fireman agreed that science does not yet know the epitope on the ADAMTS13 enzyme targeted by autoantibodies or whether the same part of the

enzyme would be targeted each time. Tr. 45-46. Therefore, "[g]iven the state of medical knowledge, it is impossible to state which precise component or antigen is the specific target of this autoimmunity [of TTP], and thus it is not feasible to isolate homology for a discussion of molecular mimicry." Pet. Ex. 23 at 7.

Although a specific molecular mimic cannot be identified, in Dr. Fireman's opinion, other available evidence, including case reports associating flu vaccine and other vaccinations with TTP, has shown "that the immune challenges that can initiate the reaction [leading to TTP] are not specific to a particular virus or bacterium" but to a list of triggers. Pet. Ex. 23 at 7. He testified that exposure to a viral antigen can cause a host response which energizes the immune system to overreact. Tr. 89. Thus, infections generally, rather than one specific infectious agent, can cause antibodies to ADAMTS13 to develop, leading to TTP. Tr. 44.

The medical community has long recognized a connection between infection and the development of TTP. *See*, *e.g.*, Pet. Ex. 39 at 2[25] ("Preceding infection, often viral, occurs in perhaps 40% of cases of TTP"); Pet. Ex. 35 at 1[26] ("Infections are well-known triggers of TTP episodes"); Pet. Ex. 38 at 2 ("The frequent acute onset of TTP associated with fever, the history of a preceding mild upper respiratory tract infection in many cases . . .has suggested an infectious etiology"); Pet. Ex. 42 at 3[27] ("Bacterial or viral infections are the most common precipitating factors for acquired TTP").

TTP has also been associated with the flu virus specifically. Dr. Fireman submitted several case reports where people developed TTP after viral flu infection.

In Kosugi et al., a 68-year-old woman with an influenza A infection developed TTP two days after having a fever. Pet. Ex. 33 at 3.[28] The authors noted that other investigators had reported that flu vaccine "may induce TTP by boosting the production of anti-ADAMTS13 autoantibodies" but autoantibody-induced TTP associated with flu infection had not yet been reported. *Id*. The authors suggested that this case report provided "the first evidence that influenza A infection alone may trigger TTP by the production of anti-ADAMTS13 IgG." *Id*. They concluded that "the present case report implies that influenza A infection triggers TTP which is almost indistinguishable from acquired idiopathic TTP by producing anti-ADAMTS13 inhibitory IgG." *Id*. at 4.

Another case report, Wasserstein et al., concerned a 50-year-old man with recurrent TTP who had a relapse "precipitated by a documented influenza infection." Pet. Ex. 39 at 1. Notably, "previous episodes occurred only during influenza epidemics, suggesting a specific relation to the

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[25] Alan Wasserstein et al., *Recurrent Thrombotic Thrombocytopenic Purpura After Viral Infection*, 141 JAMA INTERN. MED. 685-87 (1981), filed as "Pet. Ex. 39."

[26] Satoko Oka and Masaharu Nohgawa, *EB Virus Reactivation Triggers Thrombotic Thrombocytopenic Purpura in a Health Adult*, 8 LEUK. RES. REP. 1-3 (2017), filed as "Pet. Ex. 35."

[27] Young Rae Koh et al., *Thrombotic Thrombocytopenic Purpura Triggered by Influenza A Virus Subtype H1N1 Infection*, 46 TRANSFUS. APHER. SCI. 25-28 (2012), filed as "Pet. Ex. 42."

[28] Nobuharu Kosugi et al., *Influenza A Infection Triggers Thrombotic Thrombocytopenic Purpura by Producing the Anti-ADAMTS13 IgG Inhibitor*, 49 INTER. MED. 689-93 (2010), filed as "Pet. Ex. 33."

influenza agent." *Id*. at 2. The authors observed that, in keeping with an amnestic response, "A progressive increase in severity of the syndrome with each successive post viral episode in our case is consistent with sensitization to a previously experienced antigenic stimulus." *Id*.

In Jonsson et al., a 35-year-old woman who was diagnosed with TTP tested positive for influenza A infection. Pet. Ex. 40 at 1-2.[29] Although the patient did not have an additional autoimmune disorder, her blood work reflected a positive ANA. *Id*. at 2. Six months after the initial TTP episode, the patient still had a positive ANA but no other signs of a connective tissue disorder. *Id*. She later developed symptoms "indicative of an incipient unspecific connective tissue disease." *Id*. at 3. Two years after the initial TTP episode, she had a relapse of TTP associated with "an unspecified viral infection." *Id*. The authors concluded that "influenza A infection triggered development of TTP in a patient with autoimmune vulnerability." *Id*.

In Koh et al., a 27-year-old man presented to a clinic with fever, nausea, and headache for four days; he was diagnosed with pneumonia from an influenza A viral infection. Pet. Ex. 42 at 1-2. Two days later, he presented to the hospital with "fever, malaise, general weakness, headache and mental confusion." *Id*. at 2. He "had typical clinical signs of the 'pentad' diagnostic criteria of TTP and was diagnosed with TTP. *Id*. Koh noted that most inhibitory antibodies against ADAMTS13 in patients with acquired TTP are circulating IgG antibodies. *Id*. Koh further noted that acquired TTP "may be induced or triggered by various conditions," including bacterial or viral infections (specifically influenza A virus), vaccination, autoimmune disease, and certain medications. *Id*. at 2-3. Koh concluded that the influenza A subtype H1N1 infection was the most likely trigger for the patient's TTP. *Id*. at 4.

Neame, a 1980 meta-analysis of 35 studies of TTP published between 1955 and 1980, examined TTP in several contexts, including its association with other immune-related diseases, infection, and vaccination, looking at several variables in TTP, including platelet-associated IgG and complement levels. *See generally* Pet. Ex. 38. Neame observed, "TTP has occurred in days or weeks following the [preceding] infection or vaccination, and the possibility that TTP has been triggered by an immune response to vaccination or infection has been suggested." Pet. Ex. 38 at 3.

Similarly, Dr. Fireman opined that a nonviable antigen, such as a killed virus, could also provoke the production of autoantibodies to ADAMTS13 if the body recognized the immunologic structure of the antigen. Tr. 44-45. Dr. Fireman stated, based on what we know about TTP, it "make[s] sense" that the flu vaccine could cause an antibody attack on the ADAMTS13 enzyme. Tr. 46-47. Dr. Fireman acknowledged that there are no case control studies evaluating a causal connection between the flu vaccine and TTP but submitted that the case reports filed into the record were compelling and supported a causal relationship between the flu vaccine and TTP. Tr. 51, 88. To support his opinion, Dr. Fireman referenced Bitzan and Zieg, which theorized that similar to flu infections, flu vaccines may induce anti-ADAMTS13 antibodies. Tr. 52-53; Pet. Ex. 34 at 8-10[30]. Bitzan and Zieg conducted a meta-analysis of case reports of thrombotic microangiopathies

[29] Maria K. Jonsson et al., *A 35-Year-Old Woman with Influenza A-Associated Thrombotic Thrombocytopenic Purpura*, 26 BLOOD COAGUL. FIBRINOLYSIS 469-72 (2015), filed as "Pet. Ex. 40."

[30] Martin Bitzan and Jakub Zieg, *Influenza-Associated Thrombotic Microangiopathies*, 33 PEDIATR. NEPHROL. 2009-25 (2018), filed as "Pet. Ex. 34."

("TMAs"), including hemolytic-uremic syndrome ("HUS") and TTP, associated with either the flu virus or the flu vaccine. Pet. Ex. 34 at 1.

"Influenza A virus, including A(H1N1) has been invoked as a cause of TTP in at least four published reports."[31] Pet. Ex. 34 at 6. Furthermore, "Thrombotic microangiopathy has been linked to influenza vaccines in a few adults since at least 1973." Pet. Ex. 34 at 8. In an analysis of five case reports,[32] Bitzan and Zieg found, "[t]he clinical phenotype and spectrum [of] TMA (HUS, TTP) following natural influenza infections and post-vaccination are comparable." *Id*. at 8. Due to these associations, "[t]he mechanism leading to the rise of anti-ADAMTS13 and other autoantibodies by influenza and influenza vaccines warrants additional research." *Id*. at 6.

Bitzan and Zieg went on to hypothesize that, when combined with studies that have confirmed the potential of influenza virus to activate platelets and generate thrombin," "Similar to natural infections, flu vaccines may induce anti-ADAMTS13 antibodies and activate complement directly and cause HUS in patient with certain risk haplotypes." Pet. Ex. 34 at 7-9. Dr. Fireman agreed that this statement concerned HUS, which is a complement-mediated disorder, rather than TTP, which is an antibody-mediated disorder. Tr. 56-57, 97. However, he maintained that if the process of flu vaccines inducing anti-ADAMTS13 antibodies could cause HUS, it would make sense to him that the same process could cause TTP. Tr. 56-57.[33]

Two of the case reports examined by Bitzan and Zieg were submitted as literature in this matter. Brodin-Sartorius et al. examined the role of vaccination in iTTP relapse. The patient in this report was diagnosed with iTTP and recovered; "no initial factor for the onset of disease was identified (neither infection nor vaccination)." Pet. Ex. 30 at 1-3[34]. Brodin-Sartorius observed that the patient had two relapses, both preceded by flu vaccines, and noted that "although the delay might be a little long, it suggests the imputability of vaccination as a trigger." *Id*. at 2-3. The authors discussed three other cases suspecting vaccination as a trigger for TTP, occurring 24 hours after a typhoid vaccine and 15 days and four days after flu vaccine, respectively. *Id*. at 3. They further noted that, as an autoimmune disease, TTP "could be triggered by such immunologic stimulation as vaccination," and suggested that "either cross-reactive stimulation between vaccinal antigens (especially influenza vaccine) and ADAMTS 13 (sic) protease or bystander activation of vaccination with the ADAMST (sic) 13—specific immunoglobulin G causes a response." *Id*. "Furthermore, in in-vitro studies, inflammatory cytokines released the ultra-large vWF; systemic

[31] Two of the published reports were submitted as literature in this matter as Pet. Ex. 33 and Pet. Ex. 42.

[32] Two of the case reports analyzed were submitted as literature in this matter as Pet. Ex. 29 and Pet. Ex. 30.

[33] On direct examination, Dr. Fireman appeared to suggest another potential mechanism of the flu vaccine causing TTP. Tr. 58. Although the theory is not clear, it appears that he theorized that the flu virus could directly cause TTP by causing platelets to clump. *Id*. Dr. Fireman suggested this was supported by Pet. Ex. 34 at 6-7. *Id*. However, on cross examination, Dr. Fireman agreed that if the flu virus attacked platelets directly, without an attack on ADAMTS13, that would not be TTP but would be a different disorder. Tr. 99.

[34] Albane Brodin-Sartorius et al., *Recurrent Idiopathic Thrombotic Thrombocytopenic Purpura: A Role for Vaccination in Disease Relapse?* 48 AM. J. KIDNEY DIS. e31-34 (2006), filed as "Pet. Ex. 30."

inflammatory response caused by immunologic factor is another pathway linking endothelial injury and TTP." *Id*. The authors concluded, "This report emphasizes the immunologic susceptibility of TTP and from this case suggests the potential role of vaccination." *Id*. The authors recommended against additional vaccinations for this patient and suggested performing vaccinations in patient with antibodies to ADAMTS13 only when mandatory and accompanied by sustained clinical follow-up. *Id*. at 3-4.

Another case report, Dias and Gopal, discussed a 54-year-old Afro-Caribbean man who presented with "neurological signs, fever, severe thrombocytopenia, microangiopathic haemolytic anemia and renal failure 5 days after receiving an influenza vaccination." Pet. Ex. 29 at 1[35]. He was diagnosed with TTP. *Id*. The authors noted that "any other precipitating cause was excluded." *Id*. at 3. They concluded that, although "[i]solated case reports linking influenza vaccine with thrombocytopenia have been published. . . vaccination is only rarely associated with autoimmune pathology." *Id*.

According to Dr. Fireman, vaccines are an accepted immunogenic trigger for thrombocytopenia. Pet. Ex. 23 at 5. He noted that the VAERS database has been used "to demonstrate a causal link between thrombocytopenia and measles-containing vaccines." Pet. Ex. 23 at 5; Pet. Ex. 13 at 1[36] (2011 survey of 1,440 VAERS reports of thrombocytopenic purpura following vaccination from 1990 to 2008); Pet. Ex. 19 at 3[37] ("The estimated incidence of ITP-MMR is 1 in 40,000 doses. . . an incidence 6-fold higher than acute ITP of childhood"). Woo et al. found 478 reports of thrombocytopenic purpura following a measles-containing vaccine.[38] Pet. Ex. 13 at 2. Woo also found 112 reports of thrombocytopenic purpura that listed only receipt of inactivated flu vaccine. *Id*. The authors noted that "[a]utoimmune mechanisms for platelet destruction have been demonstrated" with certain medications and suggested that "[s]uch unintended immunologic effects could theoretically occur with vaccines, as well." *Id*. at 3.

Several other studies have examined the connection between the flu vaccine and ITP. Dr. Fireman discussed Shizuma,[39] a Japanese study which "described immune-mediated thrombocytopenia specifically following both influenza infections and vaccinations." Pet. Ex. 23 at 6. In Dr. Fireman's opinion, Shizuma supports a causal relationship between flu vaccine and TTP. Tr. 51. Shizuma suggested that molecular mimicry as a "probable mechanism" by which the

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[35] P.J. Dias and S. Gopal, *Refractory Thrombotic Thrombocytopenic Purpura Following Influenza Vaccination*, 64 ANAESTHESIA 444-46 (2009), filed as "Pet. Ex. 29."

[36] Emily Jane Woo et al., *Thrombocytopenia After Vaccination: Case Reports to the US Vaccine Adverse Event Reporting System, 1990-2008*, 29 VACCINE 1319-32 (2011), filed as "Pet. Ex. 13."

[37] Douglas B. Cines et al., *The ITP Syndrome: Pathogenic and Clinical Diversity*, 113 BLOOD 6511-21 (2009), filed as "Pet. Ex. 19."

[38] The Vaccine Injury Table has listed thrombocytopenic purpura occurring not less than seven days and not more than 30 days after receipt of a vaccine containing measles virus as a Table injury since 1995. *See* 42 C.F.R. § 100.3(a)(V)(A) (1995); *see also* National Vaccine Injury Compensation Program Revision of the Vaccine Injury Table, 60 Fed. Reg. 7,678 (Feb. 8, 1995).

[39] Toru Shizuma, *Immune Thrombocytopenia Following Influenza Virus Infection and Influenza Vaccine Administration*, S2 VIROL. MYCOL. OPEN ACCESS 1-4 (2014), filed as "Pet. Ex. 8."

flu vaccine could induce ITP, explaining that peptides in the flu vaccine "may elicit the cross-activation of autoreactive T or B cells." Pet. Ex. 8 at 2. "[O]n activation of B or T cells, this peptide mimic-specific immune cells cross-react with self-epitopes, thus leading to autoimmune responses such as ITP." *Id*. As noted by Dr. Fireman, Shizuma found six case reports of ITP following flu vaccine, which suggested "that the vaccinations may have been causative." Pet. Ex. 23 at 6, quoting Pet. Ex. 8 at 3.

Shizuma further noted that a German surveillance study, Garbe et al.[40], "reported that among 90 cases with at least possibly drug-induced ITP, [3.3%] were associated with influenza vaccine administration." Pet. Ex. 8 at 2. Garbe, filed as Pet. Ex. 17, concluded that in a case-control analysis, "influenza vaccination was associated with a statistically significant 4-fold risk" and recommended that "[i]n each case of newly diagnosed ITP, a drug or vaccine aetiology (sic) should be considered and a careful medication history taken." Pet. Ex. 17 at 9-10.

Shizuma also referenced a report of Evans' syndrome associated with flu vaccine; Dr. Fireman explained that Evans' syndrome is "an autoimmune condition caused by antibody response against both platelets and red blood cells, resembling a combination of both hemolytic anemia and thrombocytopenia." Pet. Ex. 23 at 6; Pet. Ex. 8 at 3. This report, authored by Shlamovitz and Johar,[41] described a 50-year-old man who developed Evans' syndrome four days after receiving a flu vaccine. Pet. Ex. 41 at 1. The authors noted that autoimmune diseases can be triggered by infections or vaccines through either antigen-specific or antigen-nonspecific mechanisms. *Id*. at 2.

It is significant that ITP has been associated with the flu vaccine because, as Dr. Fireman explained in his report, ITP and TTP are very similar diseases. Both TTP and ITP are mediated by antibody responses to specific self-antigens in the bloodstream involving T and B lymphocytes. Pet. Ex. 23 at 4. The main difference between the two conditions is the target of the antibody response. ITP involves an antibody response directly to platelets, whereas TTP results from an antibody to ADAMTS13. *Id*.

He also cited to a case report, Hendry et al.[42], where a patient suffered a relapse of aplastic anemia within one week of receiving a flu vaccine. Pet. Ex. 23 at 6; Pet. Ex. 9 at 1. Hendry suggested that the flu vaccine caused the relapse and noted that it was the authors' current practice to advise patients with aplastic anemia against having the flu vaccine. Pet. Ex. 23 at 6; Pet. Ex. 9 at 2.

In summary, Dr. Fireman opined that iTTP, an antibody-mediated autoimmune condition, results from an immunologic trigger and has been associated with infection and certain

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[40] Edeltraut Garbe et al., *Drug-Induced Immune Thrombocytopaenia: Results from the Berlin Case-Control Surveillance Study*, 68 EUR. J. CLIN. PHARMACOL. 821-32 (2012), filed as "Pet. Ex. 17."

[41] Gil Z. Shlamovitz and Sandeep Johar, *A Case of Evans' Syndrome Following Influenza Vaccine*, 44 J. EMERG. MED. e149-41 (2013), filed as "Pet. Ex. 41."

[42] C.L. Hendry et al., *Relapse of Severe Aplastic Anemia After Influenza Immunization*, 119 Br. J. Hematol. 283-84 (2002), filed as "Pet. Ex. 9."

medications. Dr. Fireman concluded that, based on case reports associating iTTP with viral flu infection as well as flu vaccines, molecular mimicry between components of the flu vaccine and epitopes on the ADAMTS13 enzyme could cause the immune system to develop autoantibodies to ADAMTS13, thus triggering iTTP.

ii. Respondent submits that literature does not support petitioner's theory

In Dr. Baumann's opinion, there is no evidence that that vaccines have a causal relationship with TTP, nor is there significant evidence that the flu vaccine can cause TTP. Tr. 145, 148.

Dr. Baumann rejected petitioner's suggested mechanism of molecular mimicry, stating that there are no studies demonstrating a homology between ADAMTS13 and the flu vaccine and researchers have not found any similarity between the ADAMTS13 structure and the structure of the flu vaccine. Tr. 126, 178. More specifically, antibodies against ADAMTS13 attack a part of the protein known as the "spacer domain." Tr. 127; Resp. Ex. P at 3 (Noting that "[a]lmost all patients" with iTTP "have anti-ADAMTS13 autoantibodies with an epitope in the spacer domain"). Researchers have tried to define what specific amino acid in the spacer domain is being recognized and attacked by autoantibodies. Tr. 127-28. This process is known as "epitope mapping." Tr. 127. According to Dr. Baumann, "[t]here is no evidence in the literature for molecular mimicry of influenza and the spacer domain of ADAMTS13." Resp. Ex. A at 4. However, Resp. Ex. P also states that many patients have anti-ADAMTS13 autoantibodies with epitopes in other ADAMTS13 domains, and "these epitopes have not been fine[ly] mapped." Resp. Ex. P at 3, 6. Although Dr. Baumann maintained that the flu vaccine could not cause autoantibodies to ADAMTS13, she agreed that the flu vaccine could trigger TTP if autoantibodies to ADAMTS13 were already present. Tr. 173-74.

When asked about Dr. Fireman's reliance on studies suggesting a possible causal connection between the wild flu virus and TTP, Dr. Baumann responded that a wild flu virus infection results in a stronger immune response than the flu vaccine. Tr. 147-48. She explained that flu infection involves "significant viral replication," which "causes tissue damage." Tr. 147-48. The tissue damage activates the innate immune system as well as complement. Tr. 148. In her opinion, the flu virus causes a much stronger response than the flu vaccine because the vaccine "doesn't reproduce and kill cells."[43] Tr. 148.

In response to Dr. Fireman's reliance on Pet. Ex. 34, which states that "flu vaccines may induce anti-ADAMTS13 antibodies and activate complement directly and cause HUS," Dr. Baumann denied any evidence exists that flu vaccines can induce ADAMTS13 antibodies. Tr. 124. She disagreed with the quoted statement and testified that the article referenced in support of that statement did not mention ADAMTS13 at all, but rather examined whether vaccinations affected levels of pre-existing autoantibodies.[44] Tr. 124-25. Unfortunately, she explained, this problem was not caught by reviewers before the paper was published. Tr. 124.

[43] Dr. Fireman agreed that the flu vaccine does not have viral replication, and the only tissue damage that results from the vaccine is the tissue damage from the injection site. Tr. 85. However, he also stated that sometimes the flu vaccine triggers the same response as wild flu infection. Tr. 85.

[44] The article referenced by Dr. Baumann was filed into the record as "Resp. Ex. Q" following the hearing.

Dr. Baumann further opined that, although TTP and HUS are both thrombotic microangiopathies ("TMAs"), they have different underlying pathologic mechanisms which distinguish the two disorders. Resp. Ex. O at 1. In other words, TTP is not comparable to HUS. Tr. 125. Dr. Baumann explained that typical HUS is caused by Shiga toxin, while atypical HUS results from uncontrolled activation of the alternative complement pathway. Resp. Ex. O at 2. Atypical HUS is primarily complement-mediated, whereas TTP is antibody-mediated. Tr. 125. Complement activation is a secondary event in TTP. Resp. Ex. O at 2. The disorders are also treated differently. HUS is treated with an anti-complement medication called Eculizimab; TTP is treated with plasma exchange, which removes the autoantibodies from the patient's blood. Tr. 120, 122. Dr. Baumann opined that, because of the differences between these two disorders, the medical literature "must be read with caution." Resp. Ex. O at 2.

She further explained that the role of von Willebrand factor in TTP was published in 1982 and ADAMTS13 was not discovered until 2001. Resp. Ex. O at 2. Therefore, in her opinion, literature submitted prior to 1982 (for example, Pet. Ex. 38) should not be relied upon because some "studies of [TMAs] completed before the discovery of ADAMTS13" may not differentiate between HUS and TTP. *Id.*

Dr. Baumann opined that there is lack of epidemiological association between the flu vaccine and TTP. Resp. Ex. A at 7. In her opinion, case control and large cohort studies provide the best data to demonstrate causal relationships. Tr. 150. She explained that a case control study would take people who had TTP and a similar number of people of similar age or demographic who don't have TTP and look at how many people in each of those groups with TTP and without TTP had the influenza vaccine prior to developing TTP. Tr. 154. In a cohort study, "we would take and follow all people who got an influenza vaccine and follow them over time and . . . similarly follow a group of people who didn't get the influenza vaccine and follow them over time and say, compare the people who did not have TTP. . . within each of those groups." Tr. 154. Dr. Baumann further testified, "TTP's incidences is quoted anywhere between two to ten per million people. So in order to get a statistically significant difference in a cohort study, you would need to follow millions upon millions of people after vaccination in order to get it." Tr. 156; *see also* Tr. 146 (Dr. Baumann's statement that "you have to follow millions and millions of people to find only one or two cases of TTP").

Dr. Baumann further submitted that Dr. Fireman's reliance on case reports and studies such as VAERS was unpersuasive. In her view, case control studies or cohort studies are more valuable epidemiological evidence than case reports. Tr. 146. She opined that case reports are useful in generating hypotheses, but not in proving causation. Resp. Ex. A at 5; *see also* Tr. 145 (case reports show only a temporal relationship), 146 (case reports are "hypothesis-generating"), 147 (case reports do not have "a high level of evidence that that is truly causal"), 151 (case reports show "a potential that we then need to further study in order to define clearly"), 155 ("In any disease or study that we're going to do, we start with a hypothesis").

Dr. Bauman explained that VAERS data contains strong biases because an adverse event is reported "only if there is a temporal relationship between the vaccination and the adverse event." Resp. Ex. A at 5. She pointed out that Pet. Ex. 13, a survey of thrombocytopenia cases reported to VAERS from 1990 to 2008, specifically excluded the six cases of TTP reported to VAERS during

that time. *Id*.; Pet. Ex. 13 at 2. She added that information in over 1000 cases of TTP worldwide from three separate registries did not note vaccination prior to any of these TTP cases. *Id*.

Dr. Baumann also raised specific objections to some of the studies cited by Dr. Fireman. In response to Dr. Fireman's reliance on Garbe et al., a German case-control study finding an increased risk of ITP after flu vaccination, she opined that studies of ITP cannot be applied to TTP. Resp. Ex. A at 4. She opined that, although they are both autoimmune disorders, they have different causes, predisposing conditions, and manifestations for thrombocytopenia in ITP and TTP. Resp. Ex. A at 4. However, in her written report, she cited to several case-control studies of ITP and flu vaccine to support her opinion that the flu vaccine cannot cause TTP. *Id*. at 5; *see also* Resp. Ex. E[45] (French case-control study finding no evidence of an increase in ITP cases following flu vaccination); Resp. Ex. I[46] (Canadian study of post-vaccination ITP in children[47] which did not include the flu vaccine); Resp. Ex. H[48] (French cohort study of 506 children with ITP; 35 had a vaccine within one month prior to onset of ITP[49]); Resp. Ex. F[50] (Surveillance study of 2.1 million U.S. veterans who received flu vaccines between October 2010 and March 2011 did not identify significant risks of GBS, ITP, or Bell's palsy following vaccination[51]).

Dr. Baumann similarly opined that a study of aplastic anemia following vaccination cannot be extrapolated to TTP due to differences in pathophysiology. Resp. Ex. A at 4. She explained that aplastic anemia is a bone marrow failure secondary to cytotoxic T-cell activation and is not antibody-mediated like TTP. *Id*. Therefore, Dr. Fireman's reference to studies addressing aplastic anemia and the recommendation to not vaccinate those with aplastic anemia is not applicable to TTP patients. *Id*. In her opinion, TTP is not a contradiction to vaccination, and she still encourages her TTP patients to get flu vaccines. Tr. 145, 180.

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[45] Lamiae Grimaldi-Besouda et al., *A Case-Control Study to Assess the Risk of Immune Thrombocytopenia Associated with Vaccines*, 120 BLOOD 4938-44 (2012), filed as "Resp. Ex. E."

[46] Laura J. Sauvé et al., *Postvaccination Thrombocytopenia in Canada*, 29 PEDIATR. INFECT. DIS. J. 559-61 (2010), filed as "Resp. Ex. I."

[47] The first sentence in this study: "There is an increasing evidence to support a link between vaccinations and thrombocytopenia, which occurs after approximately 1 in 25,000 to 1 in 40,000 doses of measles-mumps-rubella vaccine and less frequently after other vaccines." Resp. Ex. I at 2.

[48] J. Rajantie et al., *Vaccination Associated Thrombocytopenic Purpura in Children*, 25 VACCINE 1838-40 (2007), filed as "Resp. Ex. H."

[49] Dr. Baumann states in her report that none of the cases of ITP post-vaccination were associated with flu vaccine. Resp. Ex. A at 6. However, the study states that 24 children had an MMR vaccine, five children had DTP and/or polio, two children had hepatitis A or B, and four children had a vaccine that was not specified but was not MMR. Resp. Ex. H at 3.

[50] Abstract, Kwan Hur et al., *Safety of the 2010-2011 Influenza Vaccinations in the Department of Veteran Affairs*, 28 PHARMACOEPIDEMIOL. DRUG SAF. 361 (2012), filed as "Resp. Ex. F."

[51] Although this study did not find increased risk of GBS following flu vaccine, GBS occurring within three to 42 days following flu vaccine is an on-Table event.

Dr. Baumann concluded that "[v]accination has not been reported prior to onset of disease in over 1000 cases of TTP worldwide from three separate registries," and therefore, "[t]he preponderance of evidence suggests that there is not an association between the influenza vaccine and any hematologic autoimmune disease." Resp. Ex. A at 6.

iii. Analysis

For every article submitted by Dr. Fireman to support his theory, Dr. Baumann countered with a reason that the article was either inapplicable or unreliable. In her opinion, either case-controlled studies or cohort studies are required in order to support a causal relationship between the flu vaccine and TTP. Tr. 150. However, it is not petitioner's burden to provide conclusive proof, it is petitioner's burden to provide a sound and reliable theory. Dr. Baumann's standard for causation is much higher than the standard used in the Vaccine Program. Here, a petitioner is not required to produce epidemiological studies to support his theory; in fact, it would be legal error to require "conclusive evidence in the medical literature" linking the flu vaccine to TTP. *See Andreu*, 569 F.3d at 1378. As petitioner pointed out in his post-hearing brief, "There is a specific term of art within the Program for those injuries that are supported by epidemiology: it is "on-table injury."" Pet. Post-Hearing Brief at 11.

Similarly, respondent's requirement that petitioner produce an exact homology between the flu vaccine and the ADAMTS13 enzyme goes above and beyond the preponderance of the evidence standard. "[T]o require identification and proof of specific biological mechanisms would be inconsistent with the purpose and nature of the vaccine compensation program." *Knudsen*, 35 F.3d at 549. Moreover, "[t]he Court of Federal Claims is therefore not to be seen as a vehicle for ascertaining precisely how and why" a vaccine causes an injury. *Id*.; *see also Contreras v. Sec'y of Health & Human Servs.*, 107 Fed. Cl. 280, 306 (2012) ("The Federal Circuit has discouraged special masters from taking on elusive questions that science has not yet answered"). Thus, a petitioner need only show that it is more probable than not that a vaccine caused his injury, and to require this petitioner to show an exact homology would impermissibly raise his burden of proof. *Althen*, 418 F.3d at 1279.

The parties herein dispute whether the flu vaccine can trigger the development of autoantibodies to ADAMTS13, thus resulting in TTP. Unfortunately, the scientific community has not yet figured this out. *See* Pet. Ex. 11 at 5 ("In TTP, the trigger event responsible for the development anti-ADAMTS13 antibodies has not been identified yet"). A variety of infectious agents, including the flu virus, have been suggested to trigger antibodies to ADAMTS13. *Id*. There are numerous reports of both flu virus and flu vaccine as preceding immunologic triggers to TTP. *See, e.g.*, Pet. Ex. 33 at 3 (Case report of a woman with viral flu infection who developed TTP two days after a fever); Pet. Ex. 39 at 1 (Case report of a man with recurrent TTP who had a relapse after a flu infection); Pet. Ex. 40 at 1-2 (Case report of a woman with TTP triggered by viral flu infection); Pet. Ex. 42 at 1-2 (Case report of a man who presented with TTP clinical pentad six days after onset of viral flu infection); Pet. Ex. 29 at 1 (Case report of a man who presented with TTP clinical pentad five days after receiving a flu vaccine); Pet. Ex. 30 at 1-3 (Case report of four patients whose TTP was suspected to be triggered by vaccines).

Dr. Fireman opined that TTP results from an immunologic trigger and that the flu vaccine is capable of serving as this trigger. He candidly conceded that the precise mechanism by which antibodies to ADAMTS13 develop is not known but opined that exposure to antigens with molecular mimicry to ADAMTS13 was a logical trigger and that the flu vaccine was capable of setting off this process. Given the rarity of TTP as a disease and the status of research on ADAMTS13, it is not surprising that large-scale epidemiological studies demonstrating a causal relationship between the flu vaccine and TTP are not available. Instead, Dr. Fireman supported his theory with case reports, which upon review, indicate that the scientific community is continuing to inquire as to whether there is a causal link between vaccines and TTP. Based on the foregoing, I find that petitioner has provided a sound and reliable theory explaining how the flu vaccine can trigger TTP.

Accordingly, petitioner has satisfied prong I.

2. Petitioner Has Demonstrated a Logical Sequence of Cause and Effect Connecting Flu Vaccine to His Development of TTP and an Appropriate Temporal Relationship Between His Receipt of the Flu Vaccine and His Development of TTP.

To satisfy the second *Althen* prong, petitioner must demonstrate a logical sequence of cause and effect connecting the vaccine to the injury. In other words, petitioner must show that the vaccine did cause or trigger his TTP. To satisfy the third *Althen* prong, petitioner must show that injury occurred within a medically acceptable time following his vaccination. However, "[t]hat medically-acceptable time frame may be established by reliable opinion that does not perfectly match the dominant or consensus view in the medical community." *Contreras*, 107 Fed. Cl. at 303. The resolution of prongs II and III in this case are so interwoven that they are best addressed together.

Petitioner posits that the flu vaccine *did* trigger his TTP because no other trigger for his TTP was identified; his physicians attributed his TTP to the flu vaccine; and he developed symptoms of TTP within a medically appropriate time frame for vaccination. Pet. Pre-Hearing Brief at 24-25. Petitioner further submits that his malaise and fatigue were side effects of the flu vaccine rather than the first symptoms of TTP, and that his onset of TTP symptoms began one week following vaccination, when he experienced abdominal pain, shortness of breath, and hematuria. Pet. Reply Brief at 5-6.

Respondent argues that petitioner's TTP could not be caused by the flu vaccine because petitioner's TTP symptoms began three to four days after vaccination; therefore, the interval between petitioner's vaccination and his onset of TTP is "too short to have antibody production against ADAMTS13 caused by the vaccine." Resp. Pre-Hearing Brief at 5-6.

i. Petitioner submits that he had an onset of TTP symptoms seven days after vaccination, which is an appropriate temporal interval for an immune response to the flu vaccine.[52]

[52] In his post-hearing brief, petitioner alleged that he had autoantibodies to ADAMTS13 prior to his flu vaccination; however, the only evidence offered to support this allegation was a journal article noting that

Dr. Fireman opined that the flu vaccine was a substantial factor in petitioner's development of TTP. Tr. 40; Pet. Ex. 23 at 9. According to Dr. Fireman, the flu vaccine triggered the autoimmune response which led to the depletion of petitioner's ADAMTS13 enzymes and resulted in his TTP. Tr. 71-72.

According to Dr. Fireman, isolating a causal trigger for TTP is a diagnosis of exclusion. Pet. Ex. 23 at 8. Possible triggers "include infectious agents (both viral and bacterial), autoimmune diseases, cancer, and other inputs that would directly affect the immune system." *Id*. at 5. Dr. Fireman opined that symptoms of drug induced TTP occur "1 to 2 weeks following patients' exposures to an offending, immunogenic drug, although the delay in individual patients ranges from hours to several years." *Id*., citing Pet. Ex. 15 at 2-3. Dr. Fireman testified that he could not answer how long it would take for an antibody attack to manifest into the full TTP diagnostic pentad; the timing of the immune response would depend on the amount of antigen the patient was exposed to and whether the patient had prior exposure to the antigen. Tr. 48-49. He explained that prior exposure to a triggering antigen would heighten the antibody response and shorten the interval for the onset of symptoms. Tr. 50. Due to these variables, Dr. Fireman did not agree with Dr. Baumann's opinion that an antibody response would require ten to 14 days to manifest symptoms. Tr. 50.

Dr. Fireman testified that while petitioner's symptoms of generalized malaise and fatigue beginning three days after the flu shot were suggestive of TTP, he would not have conclusively diagnosed petitioner with TTP based on those symptoms. Tr. 65-66. In his view, petitioner's symptoms of abdominal pain, headaches, and hematuria five to ten days after vaccination were more specific for TTP. Tr. 66. He testified that based on these symptoms, he would have wanted to perform an evaluation including bloodwork and a urinalysis. Tr. 66. Dr. Fireman agreed that petitioner satisfied the "classical pentad" of TTP symptoms at the time he was admitted to the hospital. Tr. 67. In his opinion, petitioner's progression of symptoms was consistent with an antigen-specific antibody response. Tr. 67.

While hospitalized, petitioner's ADAMTS13 activity level was low. Pet. Ex. 3 at 348, 351 (noting that petitioner's ADAMTS13 activity was 19% and "low as expected"). Petitioner's treating physician suspected that petitioner's ADAMTS13 activity level at the time of his acute symptoms was less than 10%. *Id*. at 330. This was based on petitioner's ADAMTS13 activity level of 19% after his first plasma exchange treatment, which likely elevated his ADAMTS13 activity level. *Id*.[53]

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anti-ADAMTS13 autoantibodies have been observed in four to 15 percent of health controls and blood donors. Pet. Post-Hearing Brief at 6-7, citing Tr. 165-66; *see also* Resp. Ex. P at 6. Statistical likelihood alone is not sufficient proof to demonstrate that petitioner actually had pre-existing ADAMTS13 autoantibodies. *See Boatmon v. Sec'y of Health & Human Servs*., 941 F.3d 1351, 1363 (Fed. Cir. 2019). Because petitioner has met his burden of proof via other means, and for brevity's sake, this argument is not discussed any further herein.

[53] The fact that petitioner's ADAMTS13 level was not checked prior to treatment does not cast doubt on his claim.

Dr. Fireman noted that petitioner was not on any new drugs and had no recent infection, which are other possible triggers of TTP. Pet. Ex. 23 at 8; Tr. 67-68. More significantly, however, Dr. Fireman noted that petitioner's treating physicians attributed his TTP to the flu vaccine and found their opinions persuasive. Tr. 68-70; Pet. Ex. 3 at 348 (Oct. 29, 2013 record diagnosed TTP as possibly secondary to the flu shot); *id*. at 358 (Oct. 29, 2013 record discussing an autoimmune reaction to the flu vaccine); Pet. Ex. 1 at 5 (medical excuse note from Dr. Koenig stating petitioner had TTP secondary to the flu vaccine). He further agreed with their instruction that because of petitioner's condition, he should not receive the flu vaccine in the future. Tr. 70; Pet. Ex. 3 at 921 (record nothing that petitioner cannot be given a flu shot due to a history of flu shot induced TTP); *id*. at 1219 (hospital pharmacy record indicating that petitioner should not receive flu vaccine due to a previous reaction).

In his written report, Dr. Fireman opined that the onset of petitioner's symptoms was within one to two weeks following the vaccination, which he concluded was a medically acceptable time frame based on the medical literature. Pet. Ex. 23 at 8. Dr. Fireman acknowledged his opinion was based on an incorrect belief that the vaccine was administered on October 14, 2013, which was why he initially stated that the one to two-week onset interval was supported by medical literature. Tr. 78, 80. He testified that learning that the correct vaccination date was October 17, 2013 did not change his opinion on the causal relationship between the vaccine and petitioner's condition. Tr. 78-79. In his opinion, three days would be enough time for the immune process to generate symptoms of malaise and fatigue, and ten days was an appropriate amount of time to produce clinically acute symptoms. Tr. 60.

Dr. Fireman concluded that, "given Mr. Parmer's prior exposures to influenza, he found it consistent that Mr. Parmer experienced nonspecific symptoms three days after vaccination, that seven days would be an appropriate interval for the development of specific symptoms of TTP and that ten days would be an appropriate interval for the emergency of clinically acute symptoms." Pet. Post-Hearing Brief at 3-4, citing Tr. 60; *see also* Tr. 67; Pet. Ex. 23 at 9.

ii. Respondent's expert ultimately agreed that petitioner could have developed an immune response to the flu vaccine within seven days of vaccination.

Respondent contended that, even if the flu vaccine could induce the production of ADAMTS-13 antibodies, petitioner had an onset of symptoms three days post-vaccination, which is too short for an immune response. Joint Sub. at 3.

Dr. Baumann agreed with petitioner's diagnosis of TTP. Resp. Ex. A at 4; Tr. 117. She opined, to a reasonable degree of medical probability, that petitioner's development of TTP was an incidental event that was not caused by his flu vaccine. *Id*. at 6; Tr. 148. In her opinion, a three-day interval between the administration of the flu vaccine and the onset of TTP symptoms was too short for the flu vaccine to have caused production of an antibody against ADAMTS13 that resulted in petitioner's TTP symptoms. *Id*. Even if there were such an association, she opined that the onset of symptoms three to four days after vaccination is not a timeframe in which antibodies can form. *Id*.

Dr. Baumann testified that it takes ten to 14 days to produce antibodies against an antigen that the body has not been exposed to previously; she later stated that this process, known as primary alloimmunization, "requires at least two to three weeks." Tr. 128, 162. Peak antibody levels occur four to six weeks after exposure. Resp. Ex. A at 6. In contrast, an amnestic response to an antigen can occur if the body has seen the antigen before; because the patient has preexisting antibodies from prior exposure, new antibodies can be produced within three to ten days. Tr. 128-29, 161-62. This is known as the "booster effect." Tr. 129. She later agreed that a booster response could occur within 24 to 48 hours. Tr. 176; *see also* Resp. Ex. C at 4[54] ("This process [immune response] takes a minimum of 10-14 days but on subsequent exposure to the organism, a secondary response through activation of the various memory B cells is induced which leads to high levels of the different IgG molecules within 24-48 h[ours]").

Dr. Baumann opined that petitioner's symptoms of fatigue and malaise three days after his flu vaccination signified the onset of his TTP and were not a side effect of the vaccine. Tr. 135-36; Resp. Ex. A at 6. In her view, petitioner had a continuum of symptoms that began with fatigue and malaise and progressed to dark urine, shortness of breath, and abdominal pain. Tr. 135-36. When asked whether a patient who presented to her with malaise and fatigue three days after a flu vaccination would be evaluated for TTP, Dr. Baumann agreed that malaise and fatigue are nonspecific and can be caused by a lot of things. Tr. 157. She agreed that a person can feel tired and "off" the day after a vaccine. Tr. 136. At three days post-vaccination, the only way petitioner could have been diagnosed with TTP was if his kidney function or blood counts were checked and showed any differences. Tr. 157-58. However, Dr. Baumann has also had patients with symptoms of malaise and fatigue who were diagnosed with a viral illness before developing symptoms more specific to TTP. Tr. 158.

Dr. Baumann agreed that petitioner developed shortness of breath and abdominal pain around seven days after receipt of the flu vaccine. Tr. 136. She further agreed that petitioner had satisfied the complete clinical TTP pentad when he was admitted to the hospital ten days post-vaccination. Tr. 158. Dr. Bauman noted that although petitioner did not have neurologic symptoms prior to that day, he could have had other ongoing TTP symptoms, like hemolytic anemia; however, this is unknown, because petitioner was not checked for TTP prior to his hospital admission. Tr. 158. Dr. Baumann agreed that people of African American ancestry, like petitioner, are at higher risk for TTP. Tr. 119.

When asked whether petitioner could develop TTP symptoms within seven days of vaccination, Dr. Baumann initially testified that "for a new antibody [seven days would] be too short." Tr. 137. On further questioning, however, she instead described seven days as being "shorter than we would expect." Tr. 141-42.

iii. Analysis

In this case, petitioner's treating physicians repeatedly associated his development of TTP with the flu vaccine. Pet. Ex. 1 at 2; Pet. Ex. 2 at 12; Pet. Ex. 3 at 271, 348, 358, 889, 1219; Pet. Ex. 5 at 6, 8; Pet. Ex. 21 at 5; Pet. Ex. 54 at 25; Pet. Ex. 55 at 2. Numerous medical records support

[54] David Baxter, *Active and Passive Immunity, Vaccine Types, Excipients and Licensing*, 57 OCCUP. MED. (LOND.) 552-56 (2007), filed as "Resp. Ex. C."

petitioner's treating physicians advising against the flu vaccine in the future. Pet. Ex. 1 at 5; Pet. Ex. 3 at 921, 932, 938, 1184. The opinions of petitioner's treating physicians of an association between the flu vaccine and his development of TTP, and their recommendations against further flu vaccinations are entitled to significant weight. *Capizzano* at 1326 (recognizing that treating physicians "are likely to be in the best position to determine whether 'a logical sequence of cause and effect show(s) that the vaccination was the reason for the injury'") (quoting *Althen*, 418 F.3d at 1280).

The Federal Circuit's instruction in *Capizzano*, "which assigns probative value to the opinions of treating physicians," also applies to *Althen* prong three as "it is difficult to conceive of a treating physician who would conclude that a vaccine caused the petitioner's illness without also concluding that the onset of the illness was within a medically-acceptable time-frame." *Contreras*, 107 Fed. Cl. at 299, citing *Capizzano,* 440 F.3d at 1326. Therefore, one could prudently assume that the treating physicians who attributed petitioner's TTP to his flu vaccine also believed that there was an appropriate temporal relationship between petitioner's TTP and his flu vaccine.

The fatigue, flu-like symptoms, and generally feeling "off" described by petitioner correlate with typical side effects of the flu vaccine rather than signs of TTP. *See* Tr. 11-12, 25-26. There is a significant difference between the generalized overall discomfort petitioner initially experienced following his flu vaccination and the abdominal pain, lightheadedness, shortness of breath, hematuria, and headaches that petitioner developed one week after vaccination. *See* Tr. 13, 26; Pet. Ex. 25 at ¶ 4.

Dr. Fireman and Dr. Baumann agree that petitioner's symptoms three days following vaccination were non-specific and not necessarily indicative of TTP, as malaise and fatigue can have a variety of causes. Tr. 65-66, 157. They agree that petitioner did not satisfy the clinical pentad for TTP until he was admitted to the hospital ten days post-vaccination. Tr. 67, 158. They further agree that petitioner could have had an aberrant immune response to the flu vaccine within seven days of vaccination. Tr. 60, 67, 141-42.

Based on the petitioner's clinical presentation, the opinions of his treating physicians, and the opinions of the experts in this matter, I find that petitioner has provided a logical sequence of cause and effect explaining how the flu vaccine could have triggered his TTP, and that petitioner's TTP occurred within a medically acceptable time frame following his receipt of the flu vaccine.

Accordingly, petitioner has sustained his burden under prongs II and III.

3. Burden Shifting: Respondent Must Show an Alternative Cause of Injury

A petitioner who satisfies all three prongs of the Althen test has established a prima facie showing of causation. *Hammitt v. Sec'y of Health & Human Servs*., 98 Fed. Cl. 719 (2011). Consequently, the burden now shifts to the government to prove that an alternative cause, unrelated to the administration of the vaccine, was the "sole substantial factor" in causing the alleged injury. *De Bazan*, 539 F.3d at 1354; *see also Hammitt*, 98 Fed. Cl. at 726 (explaining that respondent's burden is to show that the "factor unrelated" was the "sole substantial factor" in causing the injury). Additionally, a factor unrelated "may not include 'any idiopathic, unexplained, unknown,

hypothetical, or undocumentable cause, factor, injury, illness or condition.'" 42 U.S.C. § 300aa-13(a)(2); *see also Doe/11 v. Sec'y of Health & Human Servs.*, 83 Fed. Cl. 157 (2008) (holding that an idiopathic diagnosis cannot be a "factor unrelated," as it is idiopathic).

Respondent has not provided evidence of any alternative cause or factor unrelated to show that petitioner's TTP was triggered or caused by a source other than vaccination. Thus, respondent has not carried his burden.

VI. Conclusion

Petitioner has presented sufficient evidence to establish that the flu vaccine he received on October 17, 2013 more likely than not caused his TTP and, therefore, he is entitled to compensation. This case shall proceed to damages.

IT IS SO ORDERED.

s/ Mindy Michaels Roth
Mindy Michaels Roth
Special Master